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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,535	10/30/2003	David T. Curiel	678503-2001.1	7880

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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,535	CURIEL ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 Dec. 2005, 24 Feb. & 07 Apr. 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-44* is/are pending in the application.

4a) Of the above claim(s) *33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-32 and 34-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's request for an interview is noted. However, the request is premature, since Applicant is not yet aware of the issues being raised in the following Office action. Applicant is respectfully referred to MPEP 713.01, section III, and MPEP 713.02, for the appropriate bases for requesting an interview.

Election/Restrictions

Newly submitted claim 33 is directed to an invention that is independent or distinct from the invention originally claimed for the reasons set forth in the Office action of 1/24/06. This claim is directed to what the specification discloses as a "conditional replication-enabling system", despite it dependence from claim 25, which excludes replication defective adenovirus such as recited in claim 33. As a result, claim 33 is improperly dependent from claim 25, as per 37 CFR 1.75(c).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 33 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The instant application is a continuation-in-part of 09/569,789. The instant application adds subject matter directed to the conditional regulation of the claimed conditionally-replicative adenovirus (CRAd) described in the '789 application wherein an adenoviral early gene is placed under control of a VEGF, survivin, or CXCR4 promoter, or where the fiber of the CRAd comprises the knob of CAV2. These new embodiments are recited specifically in claims 26 and 34-44. Claims 25 and 27-32 are generic to these embodiments. Although the generic terminology used in the instant claims is the same as used in the '789 application, the meaning of the generic terminology has changed due to the inclusion of the previously undisclosed embodiments. These new embodiments were also not described in 60/133,634. The '634 application does not describe any fiber modifications other than insertions into the HI loop. Consequently, claims 25-44 are not directed to the same invention as described in the '789 application and do not have benefit of priority to the '789 application, and the effective filing date of the instant claims is 10/30/03.

Applicant's arguments filed 12/22/05 have been fully considered but they are not persuasive. Applicant merely asserts that the priority of the claims should be 5/12/00, without providing any reasons justifying the assertion.

Claim Objections

Claims 28, 29, 34, 43 are objected to because of the following informalities.

In claim 28, --knob-- should be inserted before "domain" in line 3.

In claim 29, line 2, the "a" preceding "subtype" should be deleted; and --knob-- should be inserted before "domain" in line 3.

In claim 34, line 6, "a subtype 5" should be replaced with --an adenovirus subtype 5--. Also, in lines 12-13, "nucleotide sequence encoding" should be deleted. A VEGF promoter region is a nucleotide sequence, and is not something that is encoded.

Claims 34 and 43 (line 5 of each) recites the phrase "and hence is modified, by." This phrase is superfluous and potentially confusing, and should be deleted. Also, in claim 34 -- wherein-- should be inserted at the beginning of line 6; and a similar amendment should be made in claim 43; to provide for the transition lost by deleting the phrase.

In claim 43, lines 6 and 8, "knob domain" should be --fiber knob domain--. Also, in lines 12-13, "a nucleotide sequence encoding either CXCR4 or survivin promoters" should be replaced with -- either a CXCR4 promoter or a survivin promoter--. A CXCR4 or survivin promoter is a nucleotide sequence, and is not something that is encoded.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 34-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 34-42 are directed to a method for reducing tumor burden in a subject by administration of a modified conditionally replicative adenovirus subtype 5 "containing and expressing a nucleotide sequence encoding the fiber domain from an adenovirus subtype 3," and "contains a nucleotide sequence encoding VEGF promoter region," which causes the adenovirus to replicate in tumor cells more efficiently than in most normal cells.

In the Reply of 2/24/06, Applicant indicates that support for these amendments are found in Example 13 and Figs. 23-31. However, Example 13 describes the construction and use of a CRAd that is a modified human adenovirus subtype 5 (hAd5) where the gene encoding the fiber protein of the CRAd has the knob domain coding region replaced with a sequence encoding the knob domain of human Ad3 (hAd3). Furthermore, this replacement is to overcome the CAR-dependent infection of hAd5. Also, the E1A promoter has been replaced with a VEGF promoter region.

This originally disclosed CRAd genome does not broadly contain, at any location, and express any Ad3 "fiber domain", but specifically the hAd3 fiber knob domain and the hAd3 fiber knob coding sequence is in place of the corresponding coding sequence of the hAd5 fiber knob.

Also, the VEGF promoter is not broadly at any location in the adenoviral genome, but specifically in place of the E1A promoter and operably linked to the E1A region.

Claims 43 and 44 are directed to a method for reducing tumor burden in a subject by administration of a modified conditionally replicative "containing and expressing a nucleotide sequence encoding the knob domain of the canine adenovirus type 2," and "contains a nucleotide sequence encoding either CXCR4 or survivin promoters," which causes the adenovirus to replicate in tumor cells more efficiently than in most normal cells.

In the Reply of 2/24/06, Applicant indicates that support for these amendments are found in Example 14 and Figs. 32-35. However, Example 14 describes a prophetic CRAd that is a modified human adenovirus subtype 5 (hAd5) where the gene encoding the fiber protein of the CRAd has the knob domain coding region replaced with a sequence encoding the knob domain of canine Ad2 (Cad2). Furthermore, this replacement is to overcome the CAR-dependent infection of hAd5. Also, the Example does not specifically indicate where the CXCR4 or survivin promoter should be inserted, but implies (Fig. 34) that it should replace E1A promoter.

This originally disclosed CRAd genome does not broadly contain and express a "the [fiber] knob domain of the canine adenovirus type 2" at any location, but specifically in place of the corresponding coding sequence of the hAd5 fiber knob. Also, the CXCR4 or survivin promoter is not at any location in the adenoviral genome, but specifically in place of the E1A promoter and operably linked to the E1A region.

Consequently, the original specification does not provide evidence that the broadly claimed inventions of new claims 34 and 43, and their dependent claims, had been contemplated or possessed by the inventors at the time the application was filed. The newly presented claims

therefore contain impermissible new matter. It is suggested that the claims be amended to accurately reflect the original description of these embodiments.

Claims 25-33 and 34-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is written in a confusing manner. The claim has parts (a) and (b), and it is unclear if the adenovirus must have part (b), due to the semi-colon appearing in line 5. Also, there is lack of antecedent basis for "the modified conditionally replicative adenovirus ..." in line 5. Furthermore, claim 25 is incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are the relationship of the modified fiber protein containing the ligand and the nucleotide sequence encoding the ligand. The claim as written does not clearly indicate that the nucleotide sequence encoding the ligand is actually part of the nucleotide sequence encoding the entire modified fiber protein. These grounds of rejection apply to claims 26-32 as well. These grounds of rejection would be overcome by re-writing claim 25 as follows:

25. An infectivity-enhanced conditionally replicative adenovirus having:

(a) a modified fiber protein, said fiber protein being encoded by the genome of the adenovirus, wherein the modified fiber protein is:

i) an adenoviral fiber protein modified by the presence of a ligand comprising Arg-Gly-Asp in the HI loop of the fiber protein; or

ii) an adenoviral fiber protein modified by replacement of its fiber knob domain with a fiber knob domain from a different subtype of adenovirus;

whereby the ligand or fiber knob domain provides a pathway to cell binding by the modified conditionally replicative adenovirus other than the coxsackie-adenovirus receptor, and thereby enhances infectivity of the conditionally replicative adenovirus in tumor cells over that of wild-type adenovirus; and

(b) a tumor-specific promoter operably linked to one or more early genes selected from the group consisting of E1, E2 and E4.

Claim 34 recites the limitation "the fiber domain" in line 7, adenoviral fibers have more than one domain, and "the fiber knob domain" in line 8. There is insufficient antecedent basis for these limitations in the claim.

Claims 34-44 are incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are the relationship between the hAd3 or Cad2 fiber knob domain and their coding sequences and the modified fiber protein of the CRAd and its coding sequence. As disclosed in the specification, the coding sequences of the fiber knob domains replace the coding sequence of the fiber knob domain of a coxsackie-adenovirus receptor-dependent adenovirus on which the CRAd is based, e.g. hAd5. Such a chimeric fiber protein is encoded and expressed by the genome of the CRAd. Claims 34 and 43 should be amended to indicate that the fiber protein of the CRAd is a chimeric fiber protein comprising the hAd3 or the Cad2 fiber knob domain, respectively, and that CRAd contains and expresses a nucleotide sequence encoding the chimeric fiber protein.

Claims 34-44 are also incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element(s) is the adenoviral sequence(s) to which the VEGF promoter region (claim 34) or the "CXCR4 or surviving promoters" are operably linked such that the adenovirus replicates more efficiently in tumor cells than in most normal cells.

Claim Rejections - 35 USC § 102 & 103

Claims 25, 26, 28, 29, 34, 35 and 39 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, May 2003, as evidenced by Curiel et al., WO 00/67576.

Takayama discloses treatment of lung cancer with a CRAd comprising an E1 region under control of the human VEGF promoter and modification of its fiber by replacement of the knob with that of Ad3. Curiel is illustrative of the state of the CRAd art at the time Takayama was published, and shows that at this time one of skill in this art was aware of how to prepare CRAds and administer them in treatment of cancer. As indicated in the instant specification, the VEGF promoter is not efficient at directing transcription in normal liver cells, consequently limitation recited in claim 39 is an inherent characteristic of the this particular CRAd, which is the same CRAd as disclosed in Example 13.

Applicant's arguments filed 12/22/05 have been fully considered but they are not persuasive. Applicant argues that to the extent that this rejection is applied to the new claims, that the declaration filed should overcome the rejection because Takayama is not prior art under § 102(a). However, the declaration under 37 CFR 1.132 filed 12/22/05 is insufficient to

overcome the rejection of claims 1-5, 8, 9, 13, 15-19, 22, and 23 based upon Takayama et al. as set forth in the last Office action for the following reasons. First and foremost, the declaration (¶ 3) indicates that Takayama, Uchino, Ikegami, Reynolds, Adachi, and Kaliberova did not make an inventive contribution to the subject matter described therein, which leaves authors Krasnykh and Curiel as the "inventors" of the prior art subject matter. While Krasnykh and Curiel are named as co-inventors of the instant invention, the inventive entity of the instant application also includes Alemany and Dmitriev. Thus, the inventive entity of Takayama et al. is not the same as that of the instant application, and therefore constitutes "others under 35 USC 102(a). The declaration provides no evidence to explain this discrepancy between the apparent inventorship of the prior art subject matter in Takayama and the instant application. Such evidence might show, for example, that Alemany and Dmitriev were in fact inventors of the prior art subject matter, but for some reason were not included as co-authors of Takayama et al., or that Alemany and Dmitriev were not inventors of the prior art subject matter, but are inventors of other claimed subject matter that is not anticipated or obvious over Takayama. Alternatively, Applicant may determine upon further consideration that Alemany and Dmitriev, are not in fact inventors of the instantly claimed subject matter.

Secondly, the declaration is not properly executed. The declaration is written as a declaration by Curiel, Krasnykh, Alemany, and Dmitriev, but only Curiel and Dmitriev have signed the declaration. It is also noted the "Krashykh" in line 5 of ¶ 2 is misspelled.

Claims 25, 26, 28, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002), as evidenced by Curiel et al., WO 00/67576.

Curiel (2002) generally describes CRAd for use in treatment of cancer comprising a fiber modified by insertion of ligands into the HI loop or by replacement with the knob of an adenovirus of another serotype, wherein the E1 region of the CRAd is placed under control of a tumor specific promoter, such as the VEGF promoter, and the CRAd may contain a heterologous therapeutic gene, encoding a heat shock protein that increases increase potency of the CRAd. WO 00/67576 is illustrative of the state of the CRAd art at the time Curiel was published, and shows that at this time one of skill in this art was aware of how to prepare CRAds and administer them in treatment of cancer. Although Curiel (2002) does not explicitly disclose how the CRAd is administered, the administration routes listed claim 14 cover nearly all methods of administering CRAd.

Applicant's arguments filed 12/22/05 have been fully considered but they are not persuasive. Applicant argues that to the extent that this rejection is applied to the new claims, that the declaration filed should overcome the rejection because Curiel is not prior art under § 102(a). However, the declaration under 37 CFR 1.132 filed 12/22/05 is insufficient to overcome the rejection of claims 1-5, 8-10, 13, 15-19, and 22-23 based upon Curiel as set forth in the last Office action for the following reasons. First and foremost, the rejection is made under 35 USC 102(b), not under § 102(a) as asserted, and Curiel is a statutory bar. Second, the declaration simply indicates that Curiel is an instant co-inventor. While Curiel is named as co-inventors of the instant invention, the inventive entity of the instant application also includes Krasnykh,

Alemany and Dmitriev. Thus, the inventive entity of Curiel is not the same as that of the instant application, and therefore constitutes "others under 35 USC 102(a). Finally, the declaration is not properly executed. The declaration is written as a declaration by Curiel, Krasnykh, Alemany, and Dmitriev, but only Curiel and Dmitriev have signed the declaration.

Claims 25-27, 30-32, 34, and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takayama et al. (Mol. Ther. 7(5, Part 2): S420, abstract 1089), May 2003, in view of Curiel et al., WO 00/67576.

Takayama has been described above. In addition, Takayama teaches an embodiment wherein a HSV tk gene is co-administered with the CRAd in a "non-replicative" adenoviral vector, which produces a synergistic anti-cancer effect. Takayama does not teach to modify the fiber by insertion of an RGD-containing peptide into the HI loop or to include the HSV tk gene in the CRAd

However, Curiel teaches that as an alternative to replacing the knob portion of the fiber with that of a different adenovirus, one can overcome the reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell by genetically altering the fiber gene of the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22). Curiel also teaches to include a therapeutic gene, such a gene encoding HSV tk, in the CRAd to provide an additional means of killing tumor cells in a patient. Gancyclovir is administered following administration of the CRAd. To effect treatment of cancerous tumors, CRAds are administered intravenously , intraperitoneally, systemically, orally or intratumorally. See for example, pages 23-24.

Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Takayama by insertion of an RGD peptide into the HI loop, rather than be replacement of the fiber knob, since Curiel taught that this modification was a suitable alternative for improving infectivity of a tumor cell by a CRAd and one knew how to make such a modification. It also would have been obvious to have included the HSV tk gene in the CRAd, rather than on a separate vector, since Curiel taught that such a modification of a CRAd was useful for treating cancer, and including the tk gene in the CRAd would eliminate the necessity of preparing two separate adenovirus and improve the frequency of co-transfection of a tumor cell by both CRAd and HSV tk gene to provide an additional means to kill tumor cells.

Applicant's arguments filed 12/22/05 have been fully considered but they are not persuasive. Applicant argues that to the extent that this rejection is applied to the new claims, that the declaration filed should overcome the rejection because Takayama is not prior art under § 102(a). However, as indicated above, the declaration is insufficient to overcome Takayama.

Claims 25-27, 30-32, 34 and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002) in view of Curiel et al., WO 00/67576.

Curiel (2002) has been described above. Curiel does not teach to modify the fiber by insertion of an RGD-containing peptide, specifically, into the HI loop, to include the HSV tk gene in the CRAd.

However, WO 00/67576 teaches that one can overcome the reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell by genetically altering the fiber gene of

the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22). WO 00/67576 also teaches to include a therapeutic gene, such a gene encoding HSV tk, in the CRAd to provide an additional means of killing tumor cells in a patient. Gancyclovir is administered following administration of the CRAd. To effect treatment of cancerous tumors, CRAds are administered intravenously, intraperitoneally, systemically, orally or intratumorally. See for example, pages 23-24.

Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Curiel by insertion of an RGD peptide into the HI loop, since WO 00/67576 taught that this modification was effective for improving infectivity of a tumor cell by a CRAd and one knew how to make such a modification. It also would have been obvious to have included the HSV tk gene in the CRAd, since WO 00/67576 taught that such a modification of a CRAd was useful for treating cancer to provide an additional means to kill tumor cells. As indicated in the instant specification, the VEGF promoter is not efficient at directing transcription in normal liver cells, consequently limitation recited in claim 39 is an inherent characteristic of a CRAd whose replication is dependent upon the VEGF promoter.

Applicant's arguments filed 12/22/05 have been fully considered but they are not persuasive. Applicant argues that to the extent that this rejection is applied to the new claims, that the declaration filed should overcome the rejection because Curiel is not prior art under § 102(a). However, as indicated above, the declaration is insufficient to overcome Curiel, first and foremost because Curiel is art under § 102(b).

Claims 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Molnar-Kimber, WO 01/23004 in view of Curiel et al., WO 00/67576.

Molnar-Kimber teaches CRAds and methods of using the CRAds for the treatment of cancer (e.g. pages 8-12, claims 1-32). The CRAds comprise an E1A gene under control of a tumor specific promoter, such as the survivin promoter (e.g. page 11, ¶ 1; claims 5 and 18) to render the CRAd conditionally-replicative in tumor cells. The CRAd may also contain a therapeutic gene encoding HSV tk to augment the oncolytic activity, where gancyclovir is also administered (e.g. page 16, lines 7-12; page 30, lines 3-16). For treating cancer, the CRAd is administered intravenously, intraperitoneally, systemically, orally or intratumorally (page 31, lines 13-24). Molnar-Kimber does not teach to modify the adenoviral fiber either by insertion of an RGD peptide into the HI loop or by replacing the knob with that of a different adenovirus.

However, Curiel teaches that the loss of CAR in tumor cells reduces the infectivity by adenovirus, thereby reducing the effectiveness of treating cancer with CRAds having a wild-type fiber (page 19). Curiel teaches that this reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell can be overcome by genetically altering the fiber gene of the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22) or the knob is replaced by that of an adenovirus that binds to receptors other than CAR, e.g. of Ad3.

Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Molnar-Kimber by insertion of an RGD peptide into the HI loop or by replacement of the fiber knob with that of a different adenovirus, since Curiel taught that loss of CAR by tumor cells reduced the infectivity of CRAds (based on Ad 5) and that these

modifications of the fiber were effective for improving infectivity of a tumor cell by a CRAd, and one knew how to make such a modification.

Applicant's arguments filed 12/22/05 have been fully considered but they are not persuasive. Applicant argues only that Molnar-Kimber does not teach to modify the fiber protein and thus it would not be obvious to do so or with any expectation of success. In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection is not based on Molnar-Kimber alone, but in combination with Curiel, which provides both the motivation and the evidence of reasonable success to practice the claimed invention. Applicant has not considered the Curiel reference at all in their arguments.

Claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, May 2003, as evidenced by Curiel et al., WO 00/67576, as applied to claims 25, 26, 28, 29, 34, 35 and 39 above, and further in view of Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002.

Claims 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002) in view of Curiel et al., WO 00/67576, as applied to claims 25-27, 30-32, 34 and 39-42 above, and further in view of Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002.

Takayama et al. (2003), as evidenced by Curiel et al., has been described above, and does not teach that the method can be used to treat ovarian, gastric, and pancreatic cancers. The

combination of Curiel and Curiel et al. has been described above for teaching a CRAd with an Ad5/Ad3 chimeric fiber and VEGF promoter, and does not teach that the method can be used to treat lung cancer, such as non-small cell lung carcinoma, and ovarian, gastric, and pancreatic cancers.

However, Takayama et al. (2002) teaches that neovascularization is crucial for tumor growth and metastasis, that VEGF is well known as a key factor in tumor-associated angiogenesis, and that many different kinds of tumor exhibit increased expression of VEGF. Takayama (2002) discloses that AdVEGFE1, which is a hAd5-based CRAd having a VEGF promoter operably linked to the E1A region, is effective for killing lung, ovarian, gastric and pancreatic cancer cells, and Ad5/Ad3 VEGFE1, which is the same as AdVEGFE1 except that the fiber proteins are chimeric with a hAd3 knob domain, was even more effective in killing lung cancer cells. Takayama teaches that the mechanism of tumor-associated angiogenesis is common to many different types of cancer and that AdVEGFE1 may have universal application for treating cancer.

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have used the method of cancer treatment with an hAd5 vector having a VEGF promoter controlling its replication by operable linkage to the E1 region and a chimeric fiber protein with the knob domain of Ad3 of Takayama et al. (2003) or of Curiel and Curiel et al., to treat lung, ovarian, gastric and pancreatic cancer with a reasonable expectation of success, since Takayama (2002) taught that a CRAd having a VEGF promoter controlling replication was effective for killing these types of cancer and others, and that inclusion of the Ad3 knob domain made the CRAd even more effective for lung cancer, and since the tumor-associated

angiogenesis mechanism is common to various types of cancer, one would expect the inclusion of the Ad3 knob on the fiber protein would make it more effective on tumors of other types of cancer as well.

Claims 43 and 44 are free of the prior art of record, because it does not suggest altering the tropism of a CRAd by replacing the knob domain with that of a Cad2 fiber knob domain.

Double Patenting

Claims 25-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 9-12 of U.S. Patent No. 6,824,771 in view of Curiel et al., WO 00/67576; Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, May 2003; and Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace an obvious variant of the subject matter claimed in the '771 patent. The instant claimed invention differs from the invention of the patent primarily in the modification that renders the adenovirus conditionally-replicative. The patented invention involves mutations in E1 genes (CRAd type I), whereas the CRAd of the instant invention involves placing one or more adenoviral early genes under control of a tumor-specific promoter (CRAd type II). However, WO 00/67576 at pages 19-20, for example, discloses that type I and type II CRAds are suitable alternatives for treating cancer, and the replication selectivity of a CRAd, such as a CRAd type I or CRAd type II with only E1 genes being controlled by a tumor-specific promoter, can be improved by placing additional early genes under control of tumor-

specific promoters, such as the PSA, CEA or SLPI promoters. Curiel et al. also describes including herpes tK genes in the CRAd and treating with gancyclovir. Takayama (2003) also discloses CRAds that have a chimeric fiber, and have early genes under control of a VEGF promoter, to achieve efficient replication in tumors cells, but not normal cells, and Takayama (2002) discloses that a CRAd whose replication is directed by a VEGF promoter is effective at killing a variety of different tumor cells, such as lung, ovarian, gastric and pancreatic tumor cells, because it targets a common mechanism of tumor-associated angiogenesis.

Consequently, it would have been obvious to one of skill in the art at the time the instant invention was made to have placed early genes under control of tumor specific promoters, as instantly claimed, rather than relying upon mutations in E1 genes, as in the patented invention, to limit replication to tumors, because Curiel et al. taught that both means of promoting replication of the CRAd in tumor cells, but not in normal cells, were suitable alternatives, and that placing additional early genes under control of tumor-specific promoters further restricts viral replication to tumors and reduces its replication in normal cells.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Art Unit 1633